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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/814,292	YU ET AL.	
	Examin r	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,54,56,58-61,63-70,78,79,82,83 and 104-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,54,56,58-61,63-70,78,79,82,83 and 104-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 7/15/03 as Paper No. 20, in which several claims were amended (claims 54, 64-65 and 70) and in which claims were cancelled (claims 72-76). Claims 1-5, 54, 56, 58-61, 63-70, 78-79, 82-83, 104-107 are pending and under consideration in this action.

Any rejection of record in the previous office action not addressed herein is withdrawn. This action is not final as new grounds of rejection are added herein that were not necessitated by applicants' amendment of the claims in Paper No. 20.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 54, 56, 58-61, 63-70, 78-79, 82-83 and 104-107 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection comprises new grounds of rejection that were not necessitated by applicants' amendment of the claims in Paper No. 20.**

Each of the claims recites a limitation of a "uroplakin II (UPII) transcriptional regulatory element (TRE)" that comprises specific nucleotide sequences described in SEQ ID NO: 1 or SEQ ID NO: 2. Many of the claims are directed towards adenoviral vectors comprising an

adenoviral gene essential for replication under transcriptional control of the uroplakin II (UPII) transcriptional response element (TRE). The specification teaches that the term "transcriptional response element" refers to a promoter or enhancer that increases transcription of an operatively linked polynucleotide sequence in a cell that allows the TRE to function (page 14, lines 13-18). The specification teaches that an urothelial cell-specific TRE can comprise any number of configurations, including, but not limited to an urothelial cell-specific promoter, an urothelial cell-specific enhancer, an urothelial cell-specific promoter and heterologous enhancer, a heterologous promoter and urothelial cell-specific enhancer, and multimers of the foregoing. The promoter and enhancer components of an urothelial cell-specific TRE may be in any orientation and/or distance from the coding sequence of interest so long as the desired urothelial cell-specific expression is obtained (e.g. page 15, first paragraph). A reasonably broad interpretation of the words "uroplakin II TRE" in light of these teachings encompasses additional transcriptional regulatory elements (TREs) that are associated with the human and murine uroplakin II genes that respond under different conditions in urothelial cells (e.g. at different times during urothelial cell development) that are not present within SEQ ID NOs: 1 or 2. The claims also reasonably encompass synthetic TREs that comprise additional elements derived from homologs of UPII obtained from other sources that are not identical to those described in the specification (i.e. SEQ ID NOS: 1-2). In addition, the rejected claims encompass embodiments where the claimed enhancer only comprises portions of the largest human and murine UPII TRE elements described in the instant specification (i.e. the 2.240 kb human UPII TRE described by SEQ ID NO: 1 and the 3.592 murine UPII TRE described by SEQ ID NO: 2). Because the rejected claims are drawn towards a UPII TRE comprising only portions of the

sequences described in SEQ ID NO: 1 or 2, the rejected claims encompass a very large number of potential TRE sequences. In each case, the recited UPII TRE must retain the ability to enhance transcription of an operatively linked gene.

The specification teaches only two sequences from two different sources that are considered to be TRE sequences associated with uroplakin II genes (i.e. the 2.240 kb human UPII TRE described by SEQ ID NO: 1 and the 3.592 murine UPII TRE described by SEQ ID NO: 2). The instant specification teaches that several constructs comprising specific sequences isolated from the larger TRE elements described by SEQ ID NOS: 1 & 2 do retain at least some function in at least SW780 cells (e.g. Examples 1-2, Tables 1-2 and page 104, lines 9-21). However, the same data indicate, that at least within the context of the vector pGL3-Basic, expression of the operatively linked luciferase gene is not predictable. Constructs CP618, (comprising 600 bp 5' of the human UPII gene) and CP620 (comprising 2.0 kb 5' of the human UPII gene) demonstrate bladder-cell specific expression of the reporter gene. Construct CP619, which comprises an intermediate fragment of 1.0 kb obtained from the human UPII gene showed little expression (page 104, lines 9-21). Applicants explain these results as possibly being due to a negative regulator element located between -600 bp and -2.0 kb of the transcriptional start site that is somehow offset by an undefined sequence located more than 1.0 kb from the transcriptional start site for the UPII gene. Alternatively, one might expect that the lack of significant expression of the reporter would be due to conformational differences in the DNA in the CP619 construct as opposed to CP620 or CP618. Whatever the explanation, these data point to the complexity of enhancer element function where the presence of repressor elements or unfavorable conformation of the enhancer sequence affects activity. The results demonstrate the

unpredictability of envisioning which sequences derived from within SEQ ID NO: 1 or 2 will necessarily retain an ability to drive expression of an operatively linked gene in a given context within a given vector construct.

The instant specification does not describe any additional elements that may be associated with UPII gene expression in mice or humans during development or under different conditions. The specification does not provide a basis for one to extrapolate structural/functional characteristics of these sequences to other potential TRE sequences associated with the human and mouse uroplakin II genes that act to increase expression of the uroplakin II genes during different conditions (e.g. during different stages of animal development). The specification does not provide a basis for one to extrapolate structural/functional characteristics of the disclosed sequences of SEQ ID NO: 1 or 2 to other potential TRE sequences associated with uroplakin II genes obtained from alternative sources. The specification does not provide a reliable basis for one to envision those embodiments comprising a specific subsequence of SEQ ID NO: 1 or 2 in addition to other enhancer/promoter elements such that the synthetic construct will retain TRE activity.

The prior art does not teach the specific TRE elements described by SEQ ID NO: 1 or 2, or the characterization of the specifically recited subsequences that will retain TRE activity. The prior art does not appear to teach the characterization of different human and/or mouse uroplakin II TRE elements that are required for expression under different conditions (e.g. during embryonic development, old age, etc.) which may encompass the recited portions of SEQ ID NO: 1 or 2. The prior art does not appear to teach TRE elements from uroplakin II genes from alternative mammalian sources. Therefore, the prior art does not offset the deficiencies of the

instant specification with regard to describing the broadly claimed genus of TRE elements that retain TRE activity.

Given the very large number of potential uroplakin II TRE sequences encompassed by the rejected claims and give the lack of a basis provided by the instant specification or prior art for envisioning TRE elements associated with the human or murine uroplakin II genes and which retain TRE activity in a given context, one of skill in the art would not have been able to envision a representative number of specific embodiments to describe the broadly claimed genus of such uroplakin II TRE sequences. Therefore, one of skill in the art would have reasonably concluded that applicants were not in possession of the claimed invention.

Response to Arguments

Applicant's arguments filed on 7/15/03 in Paper No. 20 against similar grounds of rejection have been fully considered but they are not persuasive. The response essentially argues: 1) in no way should applicants be limited to "consisting of" language, 2) the fact that the claims encompass additional elements that are not recited in the claims is irrelevant as to whether applicants are entitled to the present claims, 2) the subject claims use "open" claim language and may have additional flanking sequences, but do not require any specific flanking sequence or TRE, 3) applicants are not required to describe every conceivable embodiment encompassed by the claims, 4) there is no basis for limiting sequences to "full-length" genes, 5) specific sequences retain their essential utility when operatively linked to other additional sequences, 6) in the recombinant DNA field the practical reality is that larger polynucleotide molecules into which the inventive polynucleotide of the invention can be inserted should be viewed simply as the functional milieu in which the inventive sequence can be made and used, 7) closed claim

language for nucleic acids would utterly eviscerate patent protection for those inventions, 8) open nucleic acid sequence claims are analogous to claims from other fields (e.g. open ended pharmaceutical compositions where the invention is the specific agent and not the type of formulation), 9) there is no way for applicants to obtain claims commensurate in scope with their invention except to use "comprising" language, 10) forcing applicants to limit their invention to "consisting of" language would allow anyone to easily avoid applicants' claims while taking full advantage of applicants' contribution to the art.

The examiner has at no point required applicants to describe each and every embodiment of the uroplakin II (UPII) TREs encompassed by the rejected claims. The examiner has merely pointed out the broad genus of such TRE elements encompassed by the rejected claims and the lack of a basis in the prior art and instant specification for envisioning a sufficient number of those embodiments to describe the broadly claimed genus. Applicants have defined the term "uroplakin II (UPII) TRE" in their application so broadly as to explicitly include any number of heterologous elements in any orientation or conformation. In this instance, the inclusion of the open language "comprising" is not analogous to claiming a pharmaceutical composition based on a defined agent. It is more akin to claiming a composition with a known agent that can be altered by the addition of any other active agent that has not been described except by desired effect. Nor is it analogous, for example, to including open language with a well-defined promoter sequence (e.g. the T7 promoter) because, in this case, the recited term can encompass any number of sequences (e.g. promoter elements and/or repressor elements) that change the structural/functional character of the element in ways that are not predictable. Applicants own data supports this contention.

With regard to additional sequences in combination with the specifically recited subsequences of SEQ ID NOS: 1 and 2, there is a likelihood that there are additional elements associated with the upstream regions of mouse or human UPII genes that may regulate UPII expression under different conditions (e.g. the description of a 3.6 kb region upstream of the mouse UPII coding sequence that can confer urothelial-specific gene expression (cited on pages 2-3, bridging paragraph). Given that there are multiple regulatory regions associated with the UPII genes, and given applicants own results demonstrating the complexity of transcriptional regulation with enhancer elements, it is reasonable to expect that there may be additional elements comprising at least parts of SEQ ID NO: 1 or 2 that are active under different conditions in the human or mouse. Using the suggested "consisting of" language would allow applicants to claim subsequences of SEQ ID NO: 1 or 2 that demonstrate UPII-specific TRE activity, up to and including SEQ ID NO: 1 or 2. Given the demonstrated complexity of action for enhancer sequences, the demonstrated presence of multiple and different types of enhancer elements associated with UPII genes (e.g. for the mouse gene), and the great breadth of possible TRE elements encompassed by the applicants' own definitions and the recited claims, it is not unreasonable to limit the invention to that which has been described.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

GERRY LEFFERS
PRIMARY EXAMINER

Gerald G Leffers Jr., PhD
Examiner
Art Unit 1636

Ggl